Letters to the Editor

Aspiration Thrombectomy

An Easily Forgiven "Latecomer"

We read with interest the recently published meta-analysis on the role of aspiration thrombectomy (AT) during primary percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI) (1), in which the authors reported a significantly better Thrombolysis In Myocardial Infarction (TIMI) blush grade and ST-segment resolution in the manual AT group compared with the PCI group. Consistently, they also reported a lower incidence of major adverse cardiovascular events and lower mortality in the AT group.

We agree with the editorial comment (2) that, although interesting, these results are not conclusive. In fact, the relatively smaller infarct size and near-normal left ventricular ejection fractions reported in the single studies did not allow the demonstration of conclusive clinical superiority of AT over PCI alone. This is a rather common issue affecting clinical research in the field of AMI. In fact, disappointing results can be sometimes explained through the so-called "quantitative interaction," the principle that the benefit of a given treatment is larger in high-risk patients (3). We also recognize the prognostic importance of ischemic time, which Balan and Anderson elegantly underlined in Figure 1 in their editorial comment, reporting infarct size as a function of ischemic time (2). Consequently, AT should be performed when possible and as fast as possible, like all treatments of AMI.

On the other hand, there is a further interesting aspect of manual AT that is worth reporting but that the authors missed: the beneficial effect of AT over PCI alone is higher for longer ischemic times, as shown by the meta-regression analysis we performed on the same studies analyzed by Kumbhani et al. (1), and this effect is evident for both mortality (Fig. 1A) and the rate of major adverse cardiovascular events (Fig. 1B). This phenomenon can easily be explained because we know that the efficacy of PCI rapidly decreases over time, as for all treatments of AMI, whereas AT seemingly holds its efficacy over time. Our finding is in line with a previous report by De Vita et al. (4) (Fig. 1C), showing that increasing time to treatment was associated with a significantly decreased reperfusion rate in patients treated with PCI alone, but no such trend was observed in patients treated with AT and PCI. Although no mechanism has been identified for this phenomenon, it is tempting to speculate that distal embolization may became more relevant in later stages when the thrombus is increasingly organized and more apt to disrupt in insoluble fragments. Interestingly, the MASTER (MGUARD for Acute ST Elevation Reperfusion) trial showed that the use of a mashed stent, designed to trap and exclude a thrombus, helped maintaining the efficacy of PCI over time in patients with ST-segment elevation myocardial infarction (Fig. 1C) (5).

These findings should not be misinterpreted, and the golden AMI rule "earlier is better" holds true for AT and all other treatments of AMI; however, these results suggest that AT could be of precious help in those patients with AMI who present several hours after symptom onset.

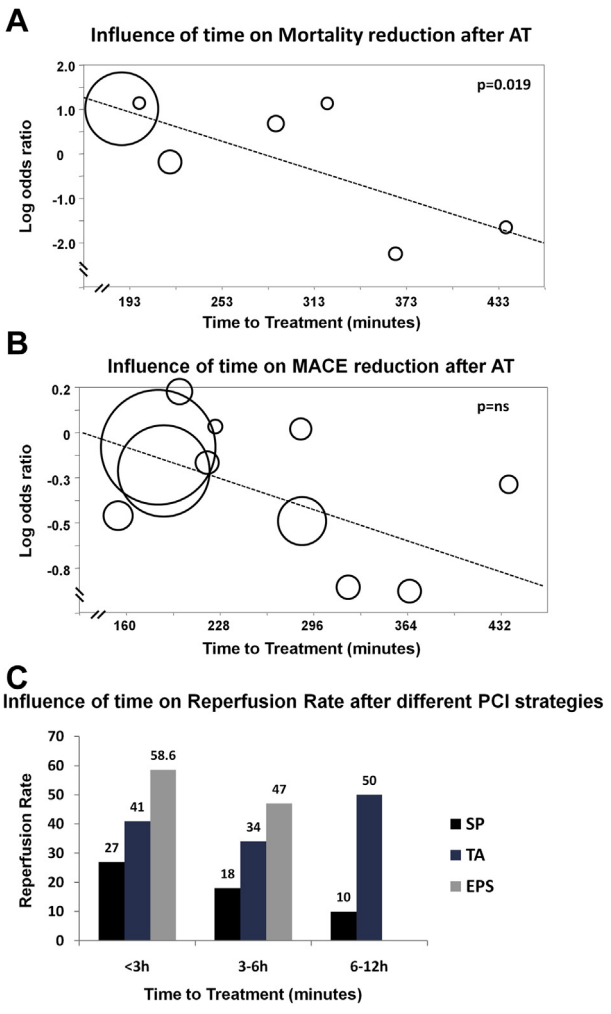

Figure 1 Influence of Reperfusion Time in Acute Coronary Revascularization

(A) Meta-regression analysis of all available studies comparing aspiration thrombectomy (AT) with standard percutaneous coronary intervention (PCI) (calculated with the unrestricted maximum likelihood model), showing a significant interaction with the time to treatment, indicating that the reduction in mortality from AT versus standard PCI is larger for longer ischemic times. Each study is represented by a **circle** that shows the effect size. The **area of each circle** is proportional to the weight of that study in the analysis. **(B)** Meta-regression analysis of all available studies comparing AT with standard PCI (calculated with the unrestricted maximum likelihood model), showing the interaction with the time to treatment, indicating that the reduction in the rate of major adverse cardiovascular events (MACE) versus standard PCI is larger for longer ischemic times. Each study is represented by a **circle** that shows the effect size. The **area of each circle** is proportional to the weight of that study in the analysis. **(C)** Rates of myocardial reperfusion in the standard PCI (SP) and thrombus aspiration (TA) groups according to time to treatment, from the study by De Vita et al. (4), and in the group of patients receiving an embolic protection stent (EPS) from the study by Dudek et al. (5). Whereas the efficacy of PCI rapidly decreases with time, prevention of distal embolization by either AT or EPS preserves the efficacy of PCI on reperfusion rate over longer times.

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Reply

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We are thankful to De Rosa and colleagues for their additional analysis of, and insight into the topic covered in our report (1). Although we were unable to directly replicate their findings, their findings are interesting and hypothesis generating. It is conceivable that aspiration thrombectomy will have a U-shaped relationship with ischemic time when more trials are included. With longer ischemic times, the thrombus becomes more organized and is subsequently harder to retrieve with manual aspiration catheters. This hypothesis should be actively investigated in future studies on this topic.

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Cardiovascular Prevention in Diabetes Mellitus

No Magic Remedies

Cardiovascular (CV) prevention has long been a target of clinical trials in diabetes mellitus (DM). Several of those trials, however, have been unsuccessful. In an effort to address this issue, the recently published PONTIAC (NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients) trial used natriuretic peptides (NPs) to select patients who had a relatively greater need for CV prevention and hence were probably more prone to improvement (1). This study was successful, but there were some questions that arise from this and previous trials on CV prevention in DM.

First, was the poor patient selection the main reason why the previous trials failed? The interventions used by some of the previous trials also may have not been successful. For example, in the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) trial, a high dose of an effective angiotensin receptor inhibitor (20 mg olmesartan) was used to prevent microalbuminuria in patients with DM who did not have hypertension, which resulted in high rates of hypotension and other complications and thus treatment failure (2,3). In the PONTIAC trial, a small but significant decline in estimated glomerular filtration rate observed in the intensified treatment group may be of some concern.

Second, what is the underlying pathophysiology for a mild increase in NP levels in symptomatic patients with DM but without known cardiac disease? There are several reasons for false-positive or negative NP results, particularly in a population such as those with DM, characterized by increased rates of comorbidities such as renal dysfunction or obesity. In other words, what is the pathogenetic process that we treat in those patients, and is the neurohormonal blockage a suitable treatment for this process? In the PONTIAC trial, there was no significant reduction in NP levels in the intensified treatment group during the study period, and thus the reason for elevated levels of NP at baseline was probably not addressed by the applied intervention.

Third, how should we titrate and monitor neurohormonal blockade therapy in patients without a clear evidence-based indication for such a therapy, such as arterial hypertension or heart failure? In the PONTIAC trial, treatment titration could not have been guided or followed by NPs, because there was no significant difference in NP levels between the 2 study groups at the end of the study.

Finally, could the positive results of the PONTIAC trial be explained solely by the increased use of health care resources in the intensified treatment group? Those patients were seen regularly not only by diabetologists but also by cardiologists in the cardiac outpatient clinics where they were receiving individualized treatment, and that may be a sufficient reason for a better outcome. In other words, the success of the PONTIAC trial may not lie on the use of NPs for patient selection but instead on the